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Treatment of IgA Nephropathy in Adults

By STEPHEN I-HONG HSU, MD, PHD

Primary or idiopathic immunoglobulin A nephropathy (pIgAN) is the most common primary glomerulonephritis worldwide. Definitive diagnosis of pIgAN is based on a single criterion – histologic evidence of predominant mesangial deposition of IgA by immunofluorescence. However, the clinical and pathologic features of pIgAN are protean, suggesting distinct subgroups with different risks for progression to end-stage renal disease (ESRD). Defining the long-term natural history of pIgAN is hampered by differences in local renal biopsy policies, the existence of distinct clinical presentations that run the spectrum from asymptomatic microscopic hematuria to rapidly progressive disease, the adoption of different pathological classification schemes, and by methodological differences in statistical analyses. These differences are reflected in a wide variability in the rate of disease progression, from 5%-25% after 10 years, and from 25%-50% after 20 years. In highly prevalent populations, pIgAN may account for 10% of incident ESRD patients. Although therapeutic trials of primarily nonspecific immunomodulatory and antiproteinuric drugs were initiated within a decade of the first description of pIgAN as a distinct disease entity by Berger and Hinglais in 1968, effective treatment regimens have not been definitively established and remain a matter of intense debate. This issue of *Nephrology Rounds* critically reviews evidence from prospective, randomized, controlled clinical trials with the goal of formulating a reasonable approach to the treatment of IgA nephropathy in adults.

In the almost 40 years since the first description of pIgAN as a distinct renal disease entity^{1,2} – one that accounts for as many as 25% to 50% of diagnoses in renal biopsy series^{3,4} – the treatment of this highly prevalent disease remains a matter of ongoing debate with many unanswered questions. Numerous therapeutic approaches have been examined in multiple independent studies, including corticosteroids alone or combined with immuno-cytoreductive agents, fish oil, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor blockers (ARBs), statins and, more recently, mycophenolate mofetil (MMF). None can be considered specific to pIgAN, since therapies targeted to pathways that underlie the immunopathogenesis of pIgAN have yet to be developed. The majority of published studies have been underpowered, with short treatment and follow-up periods, conducted on clinically-heterogeneous patients and, therefore, associated with extremely wide ranges in length of disease course and outcomes determined by the presence of poor clinical or histologic prognostic indicators at the onset and/or during the course of disease.

Although the most common presentation is microscopic hematuria or recurrent macroscopic hematuria, pIgAN may also present as nephrotic syndrome or rapidly progressive glomerulonephritis (GN), suggesting the existence of multiple disease subtypes with varying responses to a given therapy. The general paucity of completed long-term, multicenter, double-blind, randomized, placebo-controlled trials (RCTs) to establish definitive treatment options is further reflected in conflicting and variable data. The review in this issue of *Nephrology Rounds* is confined to completed and ongoing RCTs of therapy for pIgAN in adults.

Prospective RCTs of therapy for pIgAN

In a critical evaluation of completed RCTs, several themes emerge that may explain, at least in part, why these studies failed to yield definitive answers regarding therapy for pIgAN. First, the multicenter, randomized, blinded, and placebo-controlled trial is the only useful design for future therapeutic trials in pIgAN. Second, large numbers of patient cohorts with adequate follow-up periods are essential. Ultimately, clinicians need to make treatment decisions based on risk-factor profiling.

Since pIgAN is characterized by extreme variability in the clinical course, predicting the outcome for an individual patient would appear to be difficult. Fortunately, extensive reviews of numerous studies on clinical and histopathological prognostic factors by D'Amico have made clinical risk stratification feasible (Table 1).^{5,6} In general agreement with a review of 30 older studies in 2000,⁵ the more recent review of 23 studies in 2004 validated the strongest clinical predictors of

Table 1: Clinical predictors of prognosis in IgAN

D'Amico (2000)⁵ 30 Studies	D'Amico (2004)⁶ 23 Studies
Strong	Strong
<ul style="list-style-type: none"> • Impaired renal function* • High-grade proteinuria[†] (Significant by multivariate) 	<ul style="list-style-type: none"> • Impaired renal function* • High-grade proteinuria[†] • Arterial hypertension[†]
Intermediate	Weak
<ul style="list-style-type: none"> • Hypertension* (Mostly significant by univariate) 	<ul style="list-style-type: none"> • Older age* • Male gender • Absence of episodes of recurrent macrohematuria[‡] • Marked erythrocyturia[‡] (4/5)
Weak	
<ul style="list-style-type: none"> • Older age* • Male gender • Absence of episodes of recurrent macrohematuria[‡] (Significant only by univariate) 	<ul style="list-style-type: none"> * At presentation † At presentation and/or follow-up ‡ At presentation and follow-up

poor outcome on multivariate analysis. These include impaired renal function at presentation, high-grade proteinuria at presentation and/or follow-up, and arterial hypertension at presentation and/or follow-up.^{5,6} While D'Amico also found that severe histopathological disease (eg, widespread glomerulosclerosis and marked tubulointerstitial fibrosis) were strong predictors of poor outcome and that marked extracapillary proliferation was an intermediate predictor,^{5,6} clinical variables are amenable to serial measurements over time and appear to be superior to histologic grading for renal prognosis in pIgAN. The combination of mean arterial pressure (MAP) and the magnitude of proteinuria over time was superior to histologic grading in predicting the decline in creatinine clearance as a function of time.⁷ Thus, risk-factor stratification is crucial in future studies. Failure to stratify treatment groups according to their urine protein-to-creatinine ratio (UP/C), the relatively short follow-up period, and the small numbers of patients involved may have precluded a definitive conclusion in a recent and highly-anticipated RCT that evaluated omega-3 fatty acids and alternate-day prednisone in childhood pIgAN.⁸

Corticosteroids

Corticosteroids are potent anti-inflammatory agents that have been employed to treat glomerular diseases for the past 50 years. The published literature contains reports of 4 independent RCTs of corticosteroids as monotherapy in cohorts with distinct clinical presentations (ie, those with nephrotic syndrome, proteinuria without renal insufficiency, moderate histologic features, diffuse proliferative disease).⁹⁻¹²

In the earliest study, Lai et al randomized 34 pIgAN patients presenting with nephrotic syndrome¹⁰ to treatment with oral prednisolone/prednisone vs no treatment for 4 months (mons). During the mean study period of 38 mo, no significant differences in serum creatinine (SCr) and creatinine clearance were observed between comparison groups. However, the study demonstrated that steroid treatment was effective in achieving remission of nephrotic syndrome without effects on renal function in 80% of patients with mild glomerular histopathological lesions. Notably, the treatment group had significantly heavier proteinuria, while a 40% steroid-related complication rate was reported. In another study by Katafuchi et al, IgAN patients with moderate histological characteristics were treated with steroid therapy (20 mg/day [d], tapered to 5 mg/d over 2 years [yrs]). This was associated

with antiproteinuric effects, but no improvements in kidney survival. Baseline proteinuria was also significantly higher in the treatment group.⁹ In the above 2 studies, the administration of a relatively low-dose of steroids appeared to be sufficient to obtain antiproteinuric effects even in treatment groups with higher UP/Cs at baseline, as compared with controls.

Pozzi et al conducted a larger RCT in 86 consecutive pIgAN patients with urinary protein excretion rates of 1.0-3.5 g/day for at least 3 mons and plasma creatinine levels of ≤ 1.5 mg/dL.¹¹ Forty-three patients were randomized to either supportive therapy or intravenous methylprednisolone (1 g/d) for 3 consecutive days at the beginning of months 1, 3, and 5, plus alternate-day oral prednisone (0.5 mg/kg/d) for 6 mons. The comparison groups were well-matched for clinical and histological risk factors of poor outcome. In the intention-to-treat analysis, 9/43 in the steroid group vs 14/43 in the control group reached the primary endpoint of a 50% increase in plasma creatinine after a 5-yr follow-up ($P < 0.048$). Median protein excretion decreased in the steroid group, but not in the control group after 6 mons to 5 yrs of follow-up ($P < 0.05$). No side effects were reported in the steroid treatment group. These investigators published a secondary analysis of the long-term follow-up of their original study.¹³ Ten-year renal survival was significantly better in the steroid vs the control group (97% vs 53%; $P = 0.003$). One patient (2.3%) in the steroid group and 13 (30.2%) in the control group reached the endpoint of doubling baseline plasma creatinine after a median follow-up of 7 yrs. Multivariate analysis revealed that steroid therapy, a low-baseline histologic score, a reduction in proteinuria after 6 mons, and no increase in proteinuria during follow-up were independent predictors of a favorable outcome. The authors noted that there was considerable variability outside the predictive model.

Shoji et al enrolled a cohort with early IgAN (duration of urinary abnormalities < 3 yrs), proteinuria < 1.5 g/d, SCr < 1.5 mg/dL, and mesangial cell proliferation or matrix accumulation involving $> 50\%$ of glomeruli. Twenty-one patients were randomized to corticosteroids and 21 to antiplatelet therapy;¹² 19 underwent a repeat renal biopsy after 1 yr, at which time it was noted that proteinuria and histological proliferative indices, including the presence of cellular crescents, were significantly decreased only in the steroid group.

A recent meta-analysis of 6 randomized and quasi-randomized trials, including the 4 RCTs evaluated in this issue, concluded that, compared with placebo, steroids are associated with a lower risk of progression to ESRD and lower end-of-trial proteinuria.¹⁴ Although these results are based on only a few trials with very small sample sizes and potentially suboptimal methodologic quality, at present, steroids may be considered a promising and reasonable therapeutic option for intervention in patients presenting early in the course of disease with clinical risk factors indicating a poor renal outcome. However, the renoprotective effects appear to decrease in the long-term. Two ongoing RCTs of steroids plus ramipril or azathioprine, respectively, in proteinuric IgAN patients will help elucidate a more definitive role for steroids in combined therapy for improving long-term renal survival in IgAN.^{15,16}

Corticosteroids combined with cytotoxic drugs

There is anecdotal evidence for the administration of corticosteroids, plus an immuno-cytoreductive agent (eg, cyclophosphamide and/or azathioprine) primarily for patients with severe pIgAN presenting with rapidly progressive disease associated with histopathological evidence of proliferative

GN. Although several small controlled trials have been published,¹⁷ differences in study design, treatment duration, and baseline risk stratification, as well as the use of often complex and poorly-tolerated multi-drug regimens, do not allow for definitive conclusions. Locatelli et al addressed the hypothesis that early-phase treatment of progressive and proteinuric pIgAN with steroids, in combination with a well-tolerated cytotoxic agent, may be superior to steroids alone in reversing proliferative lesions and preventing the development of tubulointerstitial fibrosis.¹⁵ He initiated a long-term, multicenter, RCT of azathioprine (1.5 mg/kg/d for 6 mons) plus corticosteroids (methylprednisolone 1 g IV for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg/d for 6 mons) in comparison with corticosteroids alone.¹⁵ With a planned follow-up of 5-yrs, randomization of 255 patients was completed in 2004.¹⁷

Statins

In addition to their primary lipid-lowering properties, statins are reported to have antiproteinuric properties. Nakamura et al randomized a mixed cohort of hypercholesterolemic patients with chronic GN (27 with biopsy-proven pIgAN, 13 with diffuse mesangial proliferative GN) to cerivastatin 0.15 mg/d vs placebo for 6 mons.¹⁸ The groups were comparable according to baseline clinical variables known to be associated with poor outcome. A significant improvement in lipid profiles and a significant decrease in proteinuria and urinary podocyte excretion were observed only in the treatment group during the course of this brief trial.

Tonsillectomy

The rationale and clinical indications for tonsillectomy in pIgAN were recently reviewed.¹⁹ This invasive intervention is associated with severe pain and a potential risk for postoperative hemorrhage; nevertheless, it has been reported to improve renal survival in numerous retrospective and long-term follow-up studies performed principally in Japan. The first RCT of steroid pulses with tonsillectomy vs steroid pulses alone for the treatment of pIgAN in adults is currently underway in Japan.

Angiotensin-converting enzyme inhibitors (ACEIs)

Activation of the renin-angiotensin system (RAS) is widely considered to contribute to the final common pathway for renal disease progression, independent of underlying nephropathy. The literature contains reports of only 2 independent RCTs of ACEIs alone for the treatment of pIgAN in adults. Comparison groups were well-matched for MAP, SCr, and proteinuria in all studies. Maschio et al assessed the effect of fosinopril (20 mg/d) vs placebo in a double-blind, randomized, crossover (two 4-mon sequences), inpatient comparison of 39 normotensive and moderately proteinuric patients with preserved renal function. They reported a small, but significant, reduction in both MAP and proteinuria in the fosinopril sequence.²⁰ Praga et al randomized 44 mild-to-moderately proteinuric patients with preserved renal function to enalapril (5–40 mg/d) in order to achieve and maintain blood pressure (BP) \leq 140/90 mm Hg vs BP control with antihypertensive agents other than ACEIs or ARBs. After a mean follow-up of approximately 7 yrs, intention-to-treat analysis revealed that the primary endpoint of renal survival (50% increase in baseline SCr) was reached by 3/23 (13%) in the enalapril group and 12/21 (57%) in the control group

($P < 0.05$). Proteinuria significantly decreased in the enalapril group, while it tended to increase in the control group ($P < 0.001$). The results of one additional small RCT suggest that co-administration of urokinase and benazepril for 12 mons is superior to benazepril alone in reducing proteinuria and preserving renal function in patients with severe IgAN (defined by histopathologic findings of glomerular hypercellularity, segmental lesions and interstitial cell infiltration).²¹

There are currently 2 ongoing, multicenter, prospective RCTs examining the usefulness of an ACEI administered either alone²² or in combination with prednisone¹⁶ for the treatment of moderately proteinuric IgAN patients with “fair” renal function (creatinine clearance > 50 mL/min/d). The importance of defining the magnitude of the effect of an antihypertensive and antiproteinuric drug for the long-term treatment of a generally indolent disease, whose pathogenic mechanism likely operates over several decades, cannot be overstated. In view of the potential side effects of steroid/cytotoxic drug therapies that are administered for only short cycles and whose benefits decline over time, definitive evidence of the value of long-term ACEI therapy is critical. In addition, it is important to establish the effectiveness of ACEI therapy in order to assess the additional benefit of combined therapy with newer and more specific therapies that are likely to emerge.

Angiotensin II type 1 receptor blockers (ARBs)

In a recent multicenter, double-blind, placebo-controlled trial, 109 pIgAN patients with SCrs of 1.4–2.8 mg/dL, with or without proteinuria > 1 g/d, were randomized to treatment with valsartan 80 mg/d (titrated up to 160 mg/d to achieve and maintain BP \leq 140/90 mm Hg) vs placebo for 104 weeks.²³ Additional antihypertensive therapy was allowed to achieve the target BP in both comparison groups. The treatment group had marginally greater baseline creatinine clearance and less proteinuria than the placebo group, but neither reached statistical significance. Significantly better BP control was achieved in the valsartan group; 1/54 patients (1.9%) in the valsartan group vs 4/55 patients (7.3%) in the placebo group achieved the primary endpoint of doubling SCr or dialysis-dependent renal failure ($P = 0.21$). In a multivariate analysis, only the valsartan group achieved the secondary endpoint of a decrease in proteinuria of 33% (95% CI, 10.9–55.1). The valsartan group also exhibited a slowing of the mean rate of SCr clearance compared with placebo throughout the study period, after adjustment for average BP and proteinuria ($P = 0.014$).

An earlier RCT randomized 36 proteinuric IgAN patients (proteinuria > 1 g/d) with progressive disease (SCr < 3.0 mg/dL) to losartan (50 mg/d) vs amlodipine (5 mg/d).²⁴ Additional antihypertensive agents other than ACEIs, ARBs, and calcium channel blockers were prescribed to achieve and maintain target BP at 125/75 mm Hg during the treatment period. Both comparison groups were well-matched by MAP, creatinine clearance, and proteinuria, and achieved similar levels of target BP control. Only losartan therapy significantly reduced proteinuria ($P < 0.05$) and urinary transforming growth factor- $\beta 1$ excretion without a change in renal function.

A single ongoing multicenter, open-label, RCT has just started enrollment to examine the effectiveness of long-term blockade of the RAS with ACEI and ARB therapy, either alone or in combination, in preventing normotensive IgAN patients (aged 3–60 yrs) with normal renal function and only low-grade proteinuria (0.3–0.9 g/d) from developing progres-

sive disease.²⁵ Over 3 years, 378 patients will be randomized to ramipril, 5 mg/d (3 mg/m² in children) vs irbesartan vs supportive therapy. Combined therapy will be initiated in subjects in either treatment group if proteinuria has increased by at least 50% after 6 mons. A major aim of this study is to determine the effectiveness in a “favorable prognosis group” of treatment with a long-term and aggressive, but well-tolerated and economic, therapy for decreasing the risk of developing progressive disease, characterized by hypertension, high-grade proteinuria, and a decline in renal function.

Fish oil

Concentrated fish oil supplements are a rich source of omega-3-polyunsaturated fatty acids (ω -3-PUFA), such as eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). They have salutary effects on the production and/or activity of proinflammatory cytokines thought to mediate ongoing renal injury in pIgAN.

In 1994, the first double-blind, placebo-controlled RCTs of fish-oil therapy for the treatment of pIgAN in adults reported conflicting results.^{26,27} The studies differed significantly in design, risk stratification of comparison groups, and preparations of ω -3-PUFA. In the brief study by Pettersson et al, 32 proteinuric patients with mildly-reduced baseline renal function were randomized to the fish-oil supplement, K85, which has a high content of ω -3-PUFA (55% EPA, 30% DHA) vs corn oil, both at a dose of 6 g daily for 6 mons.²⁷ While the corn oil had no discernible effects on renal function or proteinuria, K85 was associated with a significant decline in creatinine clearance and a significant increase in SCr. In contrast, Donadio et al reported a slowing in renal disease progression in high-risk patients with IgAN.²⁶ In this 2-yr treatment study, 106 proteinuric IgAN patients with progressive disease (SCr 1.5–4.9 mg/dL; elevated in 68% of subjects at baseline) were randomized to the fish-oil supplement, Omacor (47% EPA, 37% DHA) 12 g/d, vs an olive oil placebo 12 g/d. In the fish-oil group, 3/55 patients (6%) and 14/51 patients (33%) in the placebo group reached the primary endpoint of $\geq 50\%$ increase in SCr ($P=0.002$). At the 4-yr follow-up, death or ESRD were less frequent in the fish-oil group compared with the placebo group (10% vs 40%, $P=0.006$). Similar findings were echoed in the report on 46 patients with a mean long-term follow-up to 6.4-yrs, from their earlier study, during which physicians were allowed to stop supplements, switch original placebo-assigned patients to fish oil, and continue fish oil in original fish oil-assigned patients.²⁸ A significantly greater number of nonsupplemented placebo patients developed the primary endpoint ($P=0.02$) and ESRD ($P=0.003$).

The interpretation of the above study results must take into account the unusually severe outcome observed in the original placebo group characterized by a significantly higher baseline proteinuria than the fish-oil group (3.2 ± 3.2 g/d vs 2.5 ± 1.7 g/d). This may have given the appearance of benefit in the fish-oil group due to unequal risk stratification. The low-event rate in patients with normal renal function may have also influenced the

suggestion by the authors that fish oil may be more effective in patients with impaired renal function.

Fish oil was not found to be effective for lowering proteinuria. In a subsequent multicenter, open-label RCT that randomized 73 patients to high-dose (EPA 3.76 g, DHA 2.94 g) vs low-dose (EPA 1.88 g, DHA 1.47 g) ω -3-PUFA, the two dose regimens were reported to be equivalent.²⁹ Notably, 22 of the randomized patients were assigned to placebo in the original study where the placebo arm exhibited unusually rapid disease progression;²⁶ they had significantly steeper SCr slopes than newly-enrolled patients with equivalent renal impairment at initiation of the dose-comparison trial.²⁹ Recently, a small RCT exhibiting good baseline risk stratification, randomized 14 patients to receive “very-low dose” ω -3-PUFA (EPA 0.85 g, DHA 0.57 g) vs supportive therapy and reported comparable efficacy to higher doses of ω -3-PUFA for slowing renal progression in high-risk IgAN patients, particularly those with advanced disease.³⁰ Aside from the small size of this study, the failure to demonstrate a therapeutic dose-response^{26,29,30} tends to indicate that there is no strong evidence to support the use of costly and long-term fish-oil therapy for the treatment of IgAN.

Mycophenolate mofetil (MMF)

As a better-tolerated cytotoxic agent that may have a role in modulating the humoral mechanisms believed to play key roles in the immunopathogenesis of IgAN, MMF has been assessed as a promising therapy for this disease. The published literature contains reports of 4 independent RCTs involving MMF as primary therapy (virtually all study cohorts were also receiving ACEI and/or ARB therapy),^{31–34} and 2 ongoing RCTs of MMF as part of combination therapy (ACEI therapy, with or without MMF,³⁵ and in a cohort pretreated and continually-treated with ACEI and fish oil³⁶) for the treatment of pIgAN in adults. Chen et al randomized 62 patients with severe IgAN on histology and with proteinuria levels >2.0 g/d to MMF 1.0 g/d (body weight <50 kg) or 1.5 g/d (body weight >50 kg) vs 0.8 mg/kg/d of oral prednisone.³¹ In the MMF group, overall dosage was gradually decreased to maintenance doses of ~ 1.0 g/d and ~ 0.75 g/d after 6 mons and 12 mons, respectively. At the end of the 18-mon follow-up, proteinuria was significantly reduced in the MMF group compared with the prednisone group (0.6 ± 0.7 g/d vs 1.4 ± 1.3 g/d, $P<0.05$). Notably, remission rates and total effective rates with respect to proteinuria reduction were superior in the MMF group compared with the prednisone group (44.4% vs 19.1% and 88.9% vs 61.9%, $P<0.06$, respectively). Serum cholesterol and triglycerides were only reduced in the MMF group ($P<0.05$). No patients in the MMF group exhibited significant hepatotoxicity or side effects severe enough to warrant withdrawal from therapy. Effectiveness of MMF on renal survival was not sufficiently addressed in this study to draw any conclusions.

Two small RCTs of MMF therapy have been performed in patients on strict renoprotective regimens that included dietary salt restriction and ACEI therapy. They were dosed to achieve BP targets of 125/75–85 mm Hg; however, there were conflicting results.^{33,34} Comparison

groups in both studies were well-stratified for clinical and histopathologic risk factors of disease progression.

In a single-center, placebo-controlled study, Maes et al randomized 34 IgAN patients with reduced inulin clearance (>20 , but <70 mL/min/1.73 m²) and/or proteinuria (>1 g/d/1.73 m²) and/or arterial hypertension (BP $\geq 140/90$ mm Hg on anti-hypertensive therapy) to MMF (2 g/d) vs placebo.³³ All subjects received salt restriction and ACEI therapy aimed to reach a BP target of 125/75 mm Hg. At the end of the 36-mon follow-up, no beneficial effects of 3-yr treatment with MMF were observed on renal survival or proteinuria in a patient cohort at high risk for disease progression.

In a regional two-center study, Tang et al randomized 40 IgAN patients with reduced baseline SCr (≤ 3.4 mg/dL) and persistent proteinuria (>1 g/d) despite adequate treatment with ACEI or ARB for ≥ 6 mons to achieve target BP of 125/85 mm Hg, to MMF (2 g/d for body weight ≥ 60 kg or 1.5 g/day for body weight <60 kg). This was in addition to concurrent medications vs continuation of contemporaneous medications without the addition of MMF for 24-weeks.³⁴ At the end of 72-weeks of follow-up, 16/20 patients (80%) vs 6/20 patients (30%) reached the primary endpoint of a $\geq 50\%$ reduction in proteinuria. There were no differences in BP control and renal survival between the 2 groups.

In a double-blind, placebo-controlled RCT of MMF (1.0 g/d) vs placebo for 1-yr in a small cohort of high-risk IgAN patients, with a baseline clinical and histopathologic profile similar to the study of Maes et al,³³ no benefit was seen in any outcome.³² All patients received an ACEI and/or ARB and other antihypertensives, as needed, to achieve a target BP $\leq 135/80$ mm Hg. Patients were allowed to take fish oil at their own or at their physician's discretion. The comparison groups did not differ significantly based on ACEI/ARB/fish-oil intake.

Previous RCTs have revealed a general absence of clinical benefit for MMF as an induction agent in high-risk IgAN patients with baseline moderate renal insufficiency, with or without concomitant aggressive BP control with ACEI or ARB therapy.³¹⁻³⁴ As a result, the most recently-published, single-center, prospective study of MMF examined its effectiveness as sequential maintenance therapy following initial cyclophosphamide-pulse therapy (N=18) or steroid-pulse therapy (N=2) for 6 mons in patients with advanced progressive IgAN (mean creatinine clearance 22 mL/min), who had been maintained on ACEI or ARB therapy since diagnosis.³⁷ Although MMF maintenance therapy was associated with a reduction in median loss of renal function per month, the effect was gradually lost, with a high degree of variability, such that the initial improvement or stabilization in renal function in 16/20 patients during the first 12-mons was sustained in only 10/20 patients during the 24-mon follow-up.

Two ongoing multicenter, placebo-controlled RCTs are evaluating the effectiveness of ACEI plus MMF (for 12 mons) in the course of early proteinuric IgAN with mild-moderate renal impairment³⁵ and in a similar risk cohort receiving concomitant ACEI and fish-oil therapy.³⁶ The use of MMF in combination therapy reflects the absence of an established role of MMF alone for any indication in the therapy of IgAN. The ACEI plus MMF study is planned as a 5-yr follow-up study in

which ACEI will be continued throughout.³⁵ The double-blind study examining the benefit of MMF for 1-yr in patients already receiving ACEI and fish oil, followed by an additional 1-yr follow-up will enroll children and adults.³⁶ The relatively brief duration of both therapy and follow-up, along with the inclusion of children, may lessen the chance that this study will indicate a definitive role for added benefit with MMF in the treatment of pIgAN in adults receiving long-term ACEI therapy.

Approach to the treatment of IgA nephropathy in adults

In the absence of definitive conclusions provided by reliable and consistent RCTs, an evidence-based guideline for the therapeutic management of the various clinical presentations of pIgAN most commonly encountered in the clinical setting is difficult to support. Many unanswered issues are currently being addressed by ongoing adequately-sized, well-designed RCTs that are paying meticulous attention to risk stratification and long-term follow-up. However, there is no guarantee that they will be able to achieve their aims of "proving" therapeutic efficacy. As we await the completion of these studies, the best way to approach pIgAN therapy in adults is to use reasonable and clinically useful guidelines that reflect the best available evidence, consider ongoing protocols, be aware of potential therapeutic risks, and acknowledge the likely need for well-tolerated long-term therapy. The major therapeutic goal of such a "clinical risk stratification" scheme is to minimize or normalize the major clinical risk factors associated with poor renal outcome: elevated MAP, proteinuria, and decline in renal function.

A proposed guideline for biopsy-proven pIgAN in adults is provided below:

- ACEI and ARB therapy either alone, or in combination, is the therapy of choice for all hypertensive and/or proteinuric IgAN patients (with or without hypertension). The addition of statin therapy may also work synergistically to lower proteinuria and should be initiated in all hypercholesterolemic patients.
- There is currently no strong evidence to support the use of fish-oil supplements for any indication in pIgAN in adults.
- If proteinuria is <0.5 g/d and creatinine clearance >70 mL/min, observation alone is reasonable. Alternatively, consider initiating an ACEI or ARB (even in the absence of arterial hypertension) titrated to a dose that achieves the lowest possible degree of proteinuria with the goal of completely normalizing urinary protein excretion (<0.2 g/d). There should be a minimum, once-yearly, full clinical evaluation.
- If proteinuria is >0.5 g/d and creatinine clearance >70 mL/min, initiate long-term ACEI or ARB therapy titrated to a dose that achieves the lowest possible degree of proteinuria. The goal is to completely normalize urinary protein excretion (<0.2 g/d), which may only be achievable in patients with high-grade proteinuria (eg, nephrotic syndrome) with combined ACEI/ARB/statin therapy. The aim is to achieve BP target of $\leq 125/75$ mm Hg as recommended by Disease Outcomes Quality Initiative (DOQI) guidelines for patients with renal disease and proteinuria by using combined pharma-

cotherapy (including other antihypertensive drugs, if necessary) and general measures (eg, salt-restricted diet, a weight loss regimen, moderation of alcohol intake, and smoking cessation). There should be a 3–6 mon follow-up evaluation with full clinical evaluation at 1 yr.

• If proteinuria is >1.0, but <3.0 g/d, and creatinine clearance is >70 mL/min despite maximal ACEI/ARB/statin therapy and an aggressive BP treatment regimen, consider a 6-mo. course of high-dose steroid therapy alone, with gradual taper to “off,” over a total treatment period of 12 mons. If there is no response to steroids alone, or proteinuria relapses during steroid taper, consider a course of combined therapy with steroids plus azathioprine. There should be 1–3 mo. follow-up evaluation with full clinical evaluation at 1-yr.

• If proteinuria is >3.0 g/d and/or creatinine clearance is <70 mL/min and/or creatinine clearance is rapidly declining ($\geq 15\%$ per year, typically associated with proliferative GN on histology) despite maximal ACEI/ARB/statin therapy and aggressive BP management, consider administration of a 6-mon course of combined therapy with steroids plus cyclophosphamide (or azathioprine, if cyclophosphamide is contraindicated). Consider sequential maintenance therapy with MMF or azathioprine with the length of course dictated by the initial response and subsequent clinical course; monthly follow-up evaluation with full clinical evaluation every 6 mons.

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